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Regional Variation in Out-of-Hospital Cardiac Arrest Incidence and Outcome

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IT REMAINS TO BE DETERMINED HOW often out-of-hospital cardiac arrest (OHCA) occurs. Recent sources indicate that about 166 000 to 310 000 Americans per year experience an OHCA,¹ although resuscitation is not attempted in many of these cases. The reported incidence of OHCA² and reported survival to discharge after OHCA are highly variable.³

Accurate estimation of the burden of OHCA is essential to evaluate progress toward improving public health by reducing cardiovascular disease. Clinical trials often exclude patients at higher risk of poor outcomes, so estimation of the burden of illness based only on those enrolled in trials is subject to bias. Knowledge of regional variation in outcomes after cardiac arrest could guide identification of effective interventions that are used in some communities but have not been implemented in others. Potential interventions include cultur-

Context The health and policy implications of regional variation in incidence and outcome of out-of-hospital cardiac arrest remain to be determined.

Objective To evaluate whether cardiac arrest incidence and outcome differ across geographic regions.

Design, Setting, and Patients Prospective observational study (the Resuscitation Outcomes Consortium) of all out-of-hospital cardiac arrests in 10 North American sites (8 US and 2 Canadian) from May 1, 2006, to April 30, 2007, followed up to hospital discharge, and including data available as of June 28, 2008. Cases (aged 0-108 years) were assessed by organized emergency medical services (EMS) personnel, did not have traumatic injury, and received attempts at external defibrillation or chest compressions or resuscitation was not attempted. Census data were used to determine rates adjusted for age and sex.

Main Outcome Measures Incidence rate, mortality rate, case-fatality rate, and survival to discharge for patients assessed or treated by EMS personnel or with an initial rhythm of ventricular fibrillation.

Results Among the 10 sites, the total catchment population was 21.4 million, and there were 20 520 cardiac arrests. A total of 11 898 (58.0%) had resuscitation attempted; 2729 (22.9% of treated) had initial rhythm of ventricular fibrillation or ventricular tachycardia or rhythms that were shockable by an automated external defibrillator; and 954 (4.6% of total) were discharged alive. The median incidence of EMS-treated cardiac arrest across sites was 52.1 (interquartile range [IQR], 48.0-70.1) per 100 000 population; survival ranged from 3.0% to 16.3%, with a median of 8.4% (IQR, 5.4%-10.4%). Median ventricular fibrillation incidence was 12.6 (IQR, 10.6-5.2) per 100 000 population; survival ranged from 7.7% to 39.9%, with a median of 22.0% (IQR, 15.0%-24.4%), with significant differences across sites for incidence and survival ($P < .001$).

Conclusion In this study involving 10 geographic regions in North America, there were significant and important regional differences in out-of-hospital cardiac arrest incidence and outcome.

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ally appropriate public health initiatives, community support, and equitable access to high-quality prehospital emergency care. We hypothesized that there would be significant regional variation in the incidence and outcome of OHCA.

METHODS

Design and Setting

The Resuscitation Outcomes Consortium (ROC) is a clinical research network conducting research in the areas of cardiopulmonary arrest and severe

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See also pp 1432 and 1462.

traumatic injury. This network consists of 11 sites and 1 central coordinating center. This consortium was established to evaluate the treatment of persons with life-threatening injury or OHCA and to conduct clinical trials of promising scientific and clinical advances so as to improve resuscitation outcomes. A registry (ROC Epistry–Cardiac Arrest) was created by this consortium including all cardiac arrests assessed or treated by emergency medical services (EMS) personnel in the participating geographic regions.

The ROC Epistry–Cardiac Arrest is a prospective, multicenter, observational registry of OHCA in EMS agencies and receiving institutions in 8 US sites and 3 Canadian sites.⁴ These sites are participants in the ROC clinical research network. One site that self-reported incomplete case capture (San Diego, California) was excluded from the analyses herein.

Study Population

The population of interest consisted of all OHCA cases that occurred within the catchment area of a participating EMS agency, including infants, children, and adults. The census tract of the location of the case was identified and recorded to assess the catchment population served by the agency using census data. Subgroups of the cohort included all EMS-assessed OHCA, EMS-treated OHCA, and cardiac arrests with an initial rhythm of ventricular fibrillation. Included were cases of cardiac arrest that occurred outside the hospital, were evaluated by EMS personnel and either (1) received attempts at external defibrillation (by lay responders or emergency personnel) or chest compressions by organized EMS personnel or (2) were pulseless but did not receive attempts to defibrillate or cardiopulmonary resuscitation (CPR) by EMS personnel. This latter group included patients with a do-not-attempt-resuscitation directive signed and dated by a physician, extensive history of terminal illness or intractable disease, or request from the patient's family. Traumatic injury cases were excluded.

Key Covariates

Cardiac arrests were classified as having an “obvious” cause when the circumstances and evidence clearly supported such an etiology (ie, cardiac arrest in a patient with a known toxic ingestion). Etiology was classified as “no obvious cause” for cardiac arrests for which the cause was uncertain or for which there was evidence of a primary cardiac etiology.

Some patients were initially treated with a manual defibrillator capable of recording the patient's initial rhythm. Others were initially treated with an automated external defibrillator (AED) with a built-in computer algorithm capable of classifying the patient's initial rhythm as resembling ventricular fibrillation (ie, shockable) or not (ie, not shockable). Therefore, initial rhythm was categorized as ventricular fibrillation, ventricular tachycardia, pulseless electrical activity, asystole, shockable, or not shockable. For the purpose of this analysis, ventricular fibrillation, ventricular tachycardia, and shockable rhythms were grouped together.

Data Management and Quality Assurance

Each site used multiple strategies to identify consecutive OHCA cases. Examples of case identification strategies included telephone notification of each incident defibrillator use or CPR by EMS personnel, regular hand sorting through paper EMS charts, or electronic queries of EMS records by a variety of data fields; ie, dispatch call type, vital signs, diagnosis, or a combination of these fields.

Data were abstracted from EMS records and hospital records using standardized definitions for patient characteristics, EMS process, and outcome at hospital discharge. Data were abstracted locally, coded without personal health information, and transmitted to the data coordinating center by Web entry of individual cases or batch upload of multiple cases grouped together. Site-specific quality assurance included initial and con-

tinuing education of EMS personnel in data collection. The data coordinating center ensured the quality of the data by (1) using range and logic checks in both the Web-based data entry forms and the batch upload process; (2) systematic review of data to uncover inconsistencies; (3) review of randomly selected records to confirm accuracy of data entry, and (4) annual site visits.

The study was approved under waiver of documented written consent under minimal risk criteria by 74 US institutional review boards and 34 Canadian research ethics boards as well as 26 EMS institutional review boards. In addition, approval in the form of a memorandum of understanding was obtained from 24 hospitals and from 94 EMS systems.

Outcome Measures

The annual incidence was calculated per 100 000 population for the 12-month period of May 1, 2006, to April 30, 2007. The incidence rate in persons of any age was adjusted for age and sex data from the 2000 census for the United States and 2001 census for Canada. The mortality rate was calculated as the number of known deaths per population using similar methods. The case-fatality rate was calculated as the number of known deaths divided by the total number of cases including those with missing final status. The survival rate was calculated as the number of known survivors divided by the total number of cases, including those with missing final vital status. The case-fatality rate and survival rate would only sum to 100% if final vital status were known for all patients.

Survival to discharge was defined as discharge alive from the hospital after the index OHCA. Patients transferred to another acute care facility (eg, to undergo implantable cardioverter defibrillator placement) were considered to be still hospitalized. Patients transferred to a nonacute ward or facility were considered discharged.

Statistical Analysis

We were aware before study implementation that the use of the prehospital emergency care record to abstract data for inclusion in the study databases could be associated with incomplete data due to the need for rapid treatment and consequent lack of time for EMS personnel to complete the record. A common approach to accounting for such unobserved data is to use multivariate analysis to describe observed outcomes as a function of covariates based on cases with complete data. Then outcomes are estimated for cases with incomplete data. However, this method underestimates uncertainty.⁵

Instead, we accounted for missing cases by using multiple imputation methods.⁶⁻⁸ Estimated expected cases for agency by month were determined by averaging observed cases in an agency by month based on March 2006–February 2007 data. We assumed an agency was missing cases if the observed rate was much less than expected average ($P < .005$), especially at the start of the enrollment period and at the end of the reporting year. A Poisson regression model was used within each site to estimate the expected incidence m for each month with underreported episodes for each agency. For each of 10 imputed data sets, a random draw from a Poisson distribution with mean m was used to impute the number of missing cases. For each such missing case, covariate values were then obtained through hot deck imputation using valid cases from months with good data at the corresponding agency.⁸

Baseline characteristics of EMS systems and EMS performance on cases were summarized using categorical and parametric or nonparametric descriptors as appropriate. These were reported by site.

Imputation was performed by using Excel (Microsoft Corporation, Redmond, Washington). Statistical analyses were performed by using S-PLUS version 6.2 (TIBCO Software Inc, Palo Alto,

California). Equality of rates among all sites were assessed with χ^2 tests. Two-sided P values were used. The cutoff for statistical significance was $P = .05$.

RESULTS

Ten sites were included (TABLE 1). Some of these sites include the entire named region (eg, Dallas, Texas), whereas others include several municipalities with the region (eg, Alabama). The Alabama site included 26 census county divisions. The Iowa site included 381 census county divisions. Sites had a median catchment population of 1 709 049 (interquartile range

[IQR], 958 960–2 581 569). Median population density was 698 (IQR, 405–1596) individuals per square mile. Two hundred eleven of 225 EMS agencies participating in the consortium transported patients included in this analysis to 227 of 268 receiving hospitals in the sites' catchment area. These included a mix of fire-based and non-fire-based governmental and private agencies that provided basic or advanced life support and did or did not provide patient transport.

In the total catchment population of 21.4 million (FIGURE), there were 20 520 cases of OHCA assessed by EMS.

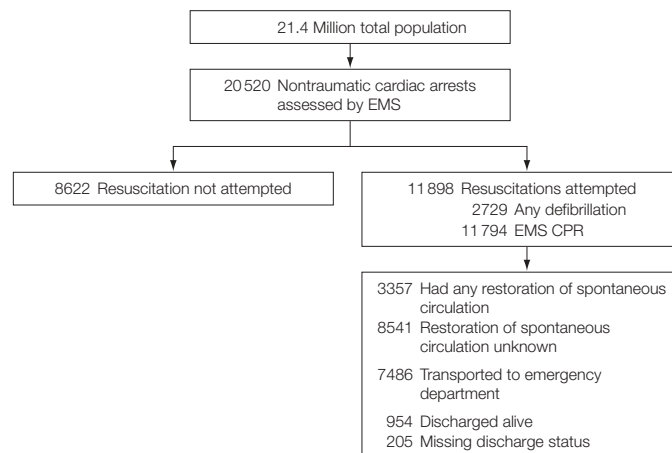
Table 1. Characteristics of Included Sites

Site	Service Area Population	Population Density, Residents per Square Mile	No. of EMS Agencies	No. of Hospitals
Alabama ^a	644 701	485	13	14
Dallas, Texas	1 989 357	3173	11	22
Iowa ^a	1 015 347	388	19	19
Milwaukee, Wisconsin	940 164	3885	16	16
Ottawa, Ontario, Canada	4 030 696	314	39	37
Pittsburgh, Pennsylvania	935 967	396	6	38
Portland, Oregon	1 751 119	431	15	16
Seattle, Washington	1 666 978	1573	35	18
Toronto, Ontario, Canada	5 627 021	911	32	55
Vancouver, British Columbia, Canada	2 779 373	1604	39	33
Total	21 398 723	640	225	268

Abbreviation: EMS, emergency medical services.

^aThe Alabama Resuscitation Outcomes Consortium (ROC) site includes 26 census county divisions within the state. The Iowa ROC site includes 381 census county divisions within the state.

Figure. Patient Flow Based on Utstein Template for Out-of-Hospital Cardiac Arrest



Resuscitation attempts include lay or emergency medical services (EMS) defibrillation and/or EMS cardiopulmonary resuscitation (CPR).

Of these, 19 920 (97.1% of total) were observed and 600 (2.9%) were imputed. These imputed cases were distributed among 12 agencies (5.7% of total) at 7 sites. Resuscitation was attempted in 11 898 cases (58.0% of total). Nine hundred fifty-four (4.6% of

total) were known to have been discharged alive.

Patient and EMS characteristics for all cases are shown in TABLE 2. Emergency medical services–assessed OHCA patients had a median age of 67 years (IQR, 53-80 years) (Table 2); 12 631

(61.6%) were men. A total of 2271 OHCA (11.1%) occurred in public locations; 2730 (13.3%) had a first recorded rhythm of ventricular fibrillation and 1887 (9.2%) had a missing or undetermined first recorded rhythm. Among EMS-treated OHCA, 1848

Table 2. Patient and EMS Characteristics of All Episodes

Characteristics	EMS-Assessed Cardiac Arrest (n = 20 520)	EMS-Treated Cardiac Arrest (n = 11 898)	Initial Rhythm VT/VF or Reported Shockable by AED (n = 2729)	Witnessed Initial Rhythm VT/VF (n = 1850)	EMS-Assessed But Not EMS-Treated (n = 8622)
Age, median (IQR), y	67 (53-80)	67 (53-79)	65 (54-76)	65 (54-76)	68 (53-81)
Unknown, No. (%)	449 (2)	92 (1)	26 (1)	13 (1)	357 (4)
Male sex, No. (%)	12 631 (61)	7550 (64)	2073 (76)	1420 (77)	5081 (59)
Unknown	183 (0.8)	27 (0.2)	5 (0.2)	4 (0.2)	156 (1.8)
Location of cardiac arrest, No. (%)					
Public	2271 (11)	1848 (16)	798 (29)	575 (31)	393 (5)
Health care setting	274 (1)	231 (2)	46 (2)	40 (2)	43 (<1)
Home/nonpublic	17 455 (85)	9773 (82)	1883 (69)	1235 (67)	7682 (89)
Unknown	520 (3)	16 (<1)	2 (<1)	0	504 (6)
First recorded rhythm, No. (%)					
VT/VF/shockable	2730 (13)	2729 (23)	2729 (100)	1850 (100)	1 (<1)
Not shockable	1086 (5)	1085 (9)	NA	NA	1 (<1)
Asystole	4793 (23)	4792 (40)	NA	NA	1 (<1)
Pulseless electrical activity	2350 (11)	2349 (20)	NA	NA	1 (<1)
Not determined	551 (3)	549 (5)	NA	NA	2 (<1)
Unknown	1336 (7)	394 (3)	NA	NA	942 (11)
No analysis by EMS	7674 (37)	NA	NA	NA	7674 (89)
Witness status					
Bystander	4728 (23)	4410 (37)	1589 (58)	1589 (86)	318 (4)
EMS	1127 (5)	1074 (9)	262 (10)	262 (14)	53 (1)
Unwitnessed	11 850 (58)	5407 (45)	724 (26)	NA	6443 (75)
Unknown	2815 (14)	1007 (9)	155 (6)	NA	1808 (21)
Bystander CPR					
Performed	3989 (19)	3739 (31)	1091 (40)	827 (45)	249 (3)
Unknown	3910 (19)	1289 (11)	222 (8)	262 (14)	2620 (30)
Time from call to first advanced life support arrival, median (IQR), min	7:00 (5:00-10:00)	7:24 (5:13-10:43)	7:15 (5:00-10:37)	8:00 (5:31-11:42)	6:11 (4:45-8:37)
Unknown, No. (%)	3995 (19)	897 (8)	195 (7)	141 (8)	3098 (36)
Time from call to first EMS rhythm analysis, median (IQR)	9:31 (7:10-12:41)	9:38 (7:18-12:49)	8:58 (6:53-11:43)	9:52 (7:34-12:55)	8:04 (6:00-11:02)
Unknown, No. (%)	9297 (45)	1622 (14)	202 (7)	87 (5)	7976 (90)
Etiology of cardiac arrest, No. (%)					
No obvious cause	17 727 (86)	10 962 (92)	2665 (98)	1810 (98)	6764 (78)
Other cause	1548 (8)	910 (8)	62 (2)	38 (2)	638 (7)
Unknown	1245 (6)	26 (<1)	3 (<1)	2 (<1)	1220 (14)
Service level of first arriving vehicle, No. (%) ^a					
BLS	698 (3)	286 (2)	64 (2)	42 (2)	412 (5)
BLS-D	8383 (41)	5269 (44)	1257 (46)	885 (48)	3055 (35)
BLS+	2584 (13)	1761 (15)	357 (13)	246 (13)	823 (10)
ALS	8732 (43)	4459 (37)	1018 (37)	655 (36)	4272 (50)
Unknown	183 (1)	123 (1)	33 (1)	0	61 (1)

Abbreviations: AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; IQR, interquartile range; NA, data not applicable; VF, ventricular fibrillation; VT, ventricular tachycardia.

^a This refers to the highest skill level of EMS providers on the first arriving vehicle. BLS (basic life support) indicates capable of performing CPR; BLS-D, capable of performing CPR and defibrillation; BLS+, capable of performing CPR and defibrillation, administering symptom relief medication, or starting intravenous therapy; ALS (advanced life support), capable of providing advanced cardiac life support, including performing endotracheal intubation, interpreting cardiac rhythm, and administering intravenous antiarrhythmic medication.

Table 3. Incidence and Outcome of EMS-Assessed Out-of-Hospital Cardiac Arrest^a

	Alabama (n = 715)	Dallas (n = 2462)	Iowa (n = 1028)	Ottawa (n = 2965)	Pittsburgh (n = 1217)	Portland (n = 1320)	Seattle (n = 2349)	Toronto (n = 5155)	Vancouver (n = 2373)	Overall (n = 19 584)
Adjusted incidence rate per 100 000	106.7	159.0	93.1	71.8	105.1	77.5	144.0	96.8	75.9	95.0
Adjusted mortality rate per 100 000	103.3	153.2	86.1	68.9	101.1	71.4	131.8	93.5	70.0	90.0
Case-fatality rate, %	96.9	96.0	92.7	96.0	96.3	92.0	91.8	96.4	92.1	94.7
Survival to discharge, %	1.1	2.4	6.1	3.3	3.3	6.5	8.1	3.2	6.7	4.4
Vital status data missing, %	2.0	1.5	1.2	0.7	0.3	1.5	0.1	0.4	1.2	0.8

Abbreviation: EMS, emergency medical services.

^aMilwaukee was excluded from this analysis because of self-reported incomplete data on patients in whom resuscitation was not attempted. All rates were unequal across sites at $P < .001$.

(15.5%) occurred in public locations; 4410 (37.0%) were witnessed by bystanders and 1074 (9.0%) by EMS personnel, 5407 (45.4%) were unwitnessed, and 1007 (8.5%) had unknown witness status. A total of 2729 (22.9%) had a first recorded rhythm of ventricular fibrillation and 3739 (31.4%) received bystander CPR. Time from call to arrival of first advanced life support was a median of 7:24 minutes (IQR, 5:13-10:43 minutes). Arrests with a first recorded rhythm of ventricular fibrillation, ventricular tachycardia, or reported as shockable by AED were similar to EMS-treated cardiac arrests except that 29.2% occurred in public locations ($P < .001$ compared with 15.5% of EMS-treated cardiac arrests).

Emergency medical services-assessed OHCA incidence and outcome are described in TABLE 3. The Milwaukee, Wisconsin site (801 treated cardiac arrests and 135 cardiac arrests with resuscitation not attempted) was excluded from this analysis because of self-reported incomplete data on patients in whom resuscitation was not attempted. There were 19 584 EMS-assessed OHCA during 20.5 million person-years of observation, resulting in an unadjusted incidence of EMS-assessed OHCA of 95.7 per 100 000 person-years. The adjusted incidence per 100 000 census population ranged from 71.8 to 159.0 (median, 96.8; IQR, 77.5-106.7). The adjusted mortality rate per 100 000 census population ranged from 68.9 to 153.2 (median, 93.5; IQR, 71.4-103.3). The known case-fatality rate ranged from

91.8% to 96.9% (median, 96.0%; IQR, 92.1%-96.3%). The known survival to discharge ranged from 1.1% to 8.1% (median, 3.3%; IQR, 3.2%-6.4%). The proportion of patients with vital status missing ranged from 0.1% to 2.0% (median, 1.2%; IQR, 0.5%-1.4%). All P values for differences in rates across sites were $< .001$.

Emergency medical services-treated OHCA is described in TABLE 4. The unadjusted incidence of EMS-treated OHCA was 55.6 per 100 000 person-years. The adjusted incidence per 100 000 census population ranged from 40.3 to 86.7 (median, 52.1; IQR, 48.0-70.1). The adjusted mortality rate per 100 000 census population ranged from 36.9 to 78.0 (median, 47.0; IQR, 42.8-60.1). The known case-fatality rate ranged from 83.5% to 93.8% (median, 90.9%; IQR, 87.3%-92.5%). The known survival to discharge ranged from 3.0% to 16.3% (median, 8.4%; IQR, 5.4%-10.4%). The proportion of patients with vital status missing ranged from 0.1% to 5.3% (median, 1.5%; IQR, 0.7%-2.4%). All P values for differences in rates across sites were $< .001$.

Incidence and outcomes associated with ventricular fibrillation are described in TABLE 5. The unadjusted incidence of ventricular fibrillation was 12.8 per 100 000 person-years. The adjusted incidence per 100 000 census population ranged from 9.3 to 19.0 (median, 12.6; IQR, 10.6-15.2). The adjusted mortality rate per 100 000 census population ranged from 7.2 to 13.7 (median, 10.1; IQR, 8.9-11.2). The known case-fatality rate ranged from 59.8% to 89.2% (median, 75.8%; IQR,

73.2%-82.9%). The known survival to discharge ranged from 7.7% to 39.9% (median, 22.0%; IQR, 15.0%-24.4%). The proportion of patients with vital status missing ranged from 0% to 7.9% (median, 2.6%; IQR, 1.1%-3.5%). All P values for differences in rates across sites were $< .001$.

COMMENT

In this large, prospective, multicenter observational study of OHCA in regions throughout North America, 7.9% of treated cardiac arrest patients and 21.0% of patients with ventricular fibrillation and cardiac arrest survived to discharge. A minority of treated cardiac arrests received bystander CPR. Incidence, mortality, case-fatality rate, and survival to discharge of EMS-assessed, EMS-treated, and ventricular fibrillation cardiac arrest cases differed significantly across geographic regions. Part of the regional differences in incidence could be attributable to differences in the completeness of case ascertainment and potential for undetected cases. However, each site had or implemented approaches to ascertain cardiac arrests from all EMS agencies within their geographic area. This prospective approach, in conjunction with statistical methods to account for missing cases, provides the most robust resource to date for determining the public health magnitude of cardiac arrest. Thus, the observed differences in incidence most likely reflect differences in the underlying risk of OHCA as well as the local approach to organized emergency

response and postresuscitation care in the hospital.

Other studies have reported regional variation in the incidence of OHCA.^{9,10} Such gradients are associated with socioeconomic and racial disparities in health. As a consequence of these gradients, cardiovascular disease is the leading cause of income-related differences in premature mortality in the United States¹¹ and Canada.¹²

It is plausible that use of secondary prevention in patients with established cardiovascular disease is more common in some regions compared with others.¹³ This would reduce the occurrence of OHCA if secondary prevention attenuated the risk of arrhythmia. Randomized trials of statin therapy^{14,15} and secondary analyses of statin use in a trial of implantable defibrillators¹⁶ demonstrate that use of such medication reduces the risk of subsequent arrest. Other studies demonstrate that β antagonists reduce the risk of death due to cardiac arrest in patients with heart failure.¹⁷ However, the magnitude of regional variation in medication use is much less than the magni-

tude of variation in cardiac arrest observed in the present study. Therefore, differences in prevention do not fully explain our findings.

Also, it is plausible that patients with symptoms of acute myocardial infarction have less delay in seeking care in some geographic regions compared with others.¹⁸ This would reduce the occurrence of infarction-related ventricular fibrillation or shift the occurrence of this rhythm to the in-hospital setting. If such differences in delay in care exist, it seems unlikely that they are due to differences in patient delay in reacting to symptoms of myocardial infarction, since interventions to modify this delay have had limited success.¹⁹ Instead, such differences could reflect regional differences in care and outcome for patients with acute cardiovascular events.^{13,20} Such differences could be reduced by implementation of systems of care for such patients.²¹ However, we observed large regional variation in survival of all EMS-treated cardiac arrests as well as in survival of the minority of cardiac arrests that were due to ventricular fibrillation and potentially associated

with acute myocardial infarction. Therefore, regional variation in care for acute cardiovascular events does not fully explain our findings.

Other investigators^{22,23} have reported survival rates ranging from 0% to 21% after treatment of OHCA. Emergency medical services agencies in large cities have special challenges in achieving good outcomes after cardiac arrest.^{24,25} Our analysis suggests that such differences do not reflect interstudy differences in inclusion criteria or outcome definition, because each site in the present study implemented uniform definitions of cardiac arrest and survival. It seems likely that these differences reflect, in part, regional differences in the availability of emergency cardiac care.²⁶ These differences include bystander CPR, lay responder defibrillation programs,²⁷ EMS factors such as experience of personnel,²⁸ and types of interventions provided by EMS personnel^{29,30} or treatments available at receiving hospitals.^{31,32} Some of these factors have been associated with differences in survival or quality of life after resuscitation,^{3,33-35} although no analysis has had adequate power to

Table 4. Incidence and Outcome of EMS-Treated Out-of-Hospital Cardiac Arrest^a

	Alabama (n = 267)	Dallas (n = 1265)	Iowa (n = 565)	Milwaukee (n = 801)	Ottawa (n = 1836)	Pittsburgh (n = 575)	Portland (n = 793)	Seattle (n = 1170)	Toronto (n = 2992)	Vancouver (n = 1634)	Overall (n = 11 898)
Adjusted incidence rate per 100 000	40.3	82.9	51.3	86.7	45.1	51.1	47.0	74.4	57.0	52.8	56.0
Adjusted mortality rate per 100 000	36.9	77.2	44.4	78.0	42.3	47.1	41.0	62.3	53.6	46.9	50.9
Case-fatality rate, %	91.7	92.6	86.9	90.1	93.5	92.3	86.8	83.5	93.8	88.5	90.7
Survival to discharge, %	3.0	4.5	11.0	9.7	5.3	7.0	10.6	16.3	5.5	9.7	7.9
Vital status data missing, %	5.3	2.9	2.1	0.1	1.2	0.7	2.5	0.2	0.7	1.7	1.4

Abbreviation: EMS, emergency medical services.

^aAll rates were unequal across sites at $P < .001$.

Table 5. Incidence and Outcome of Ventricular Fibrillation^a

	Alabama (n = 65)	Dallas (n = 195)	Iowa (n = 135)	Milwaukee (n = 165)	Ottawa (n = 429)	Pittsburgh (n = 102)	Portland (n = 249)	Seattle (n = 297)	Toronto (n = 614)	Vancouver (n = 478)	Overall (n = 2729)
Adjusted incidence rate per 100 000	9.9	12.8	12.4	18.7	10.4	9.3	15.1	19.0	11.4	15.2	12.8
Adjusted mortality rate per 100 000	8.8	10.7	8.9	13.7	8.6	7.2	11.3	11.5	9.5	10.9	9.8
Case-fatality rate, %	89.2	82.7	72.9	74.0	83.1	77.5	73.9	59.8	83.0	71.7	76.5
Survival to discharge, %	7.7	9.5	22.7	26.0	14.8	21.5	22.5	39.9	15.7	25.0	21.0
Vital status data missing, %	3.1	7.9	4.4	0	2.1	1.0	3.6	0.3	1.3	3.3	2.5

^aAll rates were unequal across sites at $P < .001$.

detect the independent contributions of these factors.

Morbidity and mortality from most cardiovascular diseases have declined over the last 30 years.³⁶ The majority of this reduction has been attributed to risk factor modification.³⁷ However, there has been little improvement in the incidence of OHCA survival during this same period.^{38,39} Experts have proposed that OHCA should be designated a reportable event to facilitate monitoring and improvement of cardiovascular health.⁴⁰ The present study demonstrates that large regional differences in OHCA epidemiology exist and are a prelude to further analysis to understand the causes of these variations as well as implementation of targeted interventions to reduce them. The discordance between case-fatality rate and survival to discharge underscores the importance of complete ascertainment of vital status as national, public reports of OHCA incidence and outcome become available.

Cardiovascular disease is the leading cause of death in the United States.¹ The Institute of Medicine has identified the need to improve funding for EMS operations.⁴¹ Extrapolation of the mortality rate observed in the study regions to the total population of the United States suggests that as many as 294 851 (quasi confidence interval, 236 063-325 007) EMS-assessed OHCA cases may occur annually in the United States (96.8 per 100 000 \times 304 598 626 [US population]). (Quasi confidence intervals were calculated by using the IQR for the mortality rate multiplied by the total population of the country.) Extrapolation of this study to the total population of Canada suggests that as many as 32 160 (quasi confidence interval, 25 748-35 450) EMS-assessed OHCA cases may occur annually in Canada (96.8 per 100 000 \times 33 223 840 [Canadian population]). Collectively, these estimates of burden imply that allocation of increased resources for EMS operations is necessary to achieve important improvements in cardiovascular health in either country.

If survival after OHCA treated by EMS could be increased throughout North America from the study average of 7.9% to the maximum observed rate of 16.3%, an estimated 15 000 premature deaths would be prevented each year (52.1 per 100 000 \times [304 598 626 + 33 223 840] \times [16.3% - 7.9%]). Ongoing funding for fundamental, translational, and clinical research related to emergency cardiovascular care is necessary to ensure that such improvements in public health can be achieved.

This study has several strengths compared with previous studies. Clinical trials often exclude patients at higher risk of poor outcomes, so estimation of the burden of illness based only on those enrolled in trials is subject to bias. Existing OHCA registries do not contain the necessary information to determine which interventions are effective in the out-of-hospital setting. Several large regional registries have evaluated the effectiveness of out-of-hospital interventions on outcomes after OHCA.^{42,43} However, these studies may have underestimated the incidence of OHCA because they excluded individuals who are assessed but not treated by EMS personnel.

This study has several limitations. First, sites for this registry were selected by a competitive process emphasizing regional sites with well-organized EMS systems and associated investigators, so results observed in participating sites may not be representative of the community at large. However the catchment population of participating communities includes approximately 10% of the North American population and has diverse geographic and socioeconomic characteristics. To the best of our knowledge, this population is larger than that of any other ongoing OHCA registry.

Second, it is plausible that incidence, structure, process, and outcome data reported by each site are subject to ascertainment bias because not all responses are audited. However, all sites agreed to the data elements be-

fore study initiation, trained data collection personnel, and altered existing paper or electronic data capture to increase the likelihood of data capture. Moreover, our use of timely episode reporting by sites facilitates quick feedback from the coordinating center to sites and to responders to reduce the amount of incomplete data.

Third, the expected number of OHCA cases was not observed for some agencies during specific time intervals within the sampling period. Multiple imputation was used to account for such missing data. This approach allows better estimation of the variability of the data and helps to ensure appropriately proportionate weight for each agency. This method assumes that the cases randomly imputed, which in our case were from the same agency in a different time period, have the same patient, EMS process, and outcome characteristics as the missing data. Registry data have not shown any significant time trends that would bias this imputation process.⁴⁴ Furthermore, only a small proportion of the total cases were imputed in this study, so it seems unlikely that this imputation would reduce its validity.

Fourth, we were unable to assess the effect of hospital-based postresuscitation care on outcomes after OHCA because of our lack of patient-specific data about processes of care delivered in the hospital. In-hospital therapeutic hypothermia improves outcomes after OHCA.³¹ A small trial suggested that hemofiltration to reduce inflammation after OHCA offers additional benefit.⁴⁵ Observational studies suggest that early percutaneous coronary intervention improves outcomes as well.^{46,47} Therefore, future assessments of regional variation in outcome after OHCA should assess the relative effects of out-of-hospital and hospital-based care.

Fifth, we also were unable to report on neurologic outcome at discharge. Assessment of Cerebral Performance Category (CPC) at discharge is a recommended part of resuscitation outcome studies.⁴⁸ However, the CPC has

limited discrimination between mild and moderate brain injury. A small study with incomplete follow-up of survivors demonstrated only moderate correlation with other measures of health-related quality of life.⁴⁹ Although a larger study demonstrated a better correlation between CPC and generic measures of health-related quality of life, CPC should not be considered a substitute for reliable and valid measures of the latter.⁵⁰ Nonetheless, previous studies demonstrate that resuscitation interventions that are associated with better survival are also associated with better quality of life.^{34,35}

These findings have implications for prehospital emergency care. The 5-fold variation in survival after EMS-treated cardiac arrest and 5-fold variation in survival after ventricular fibrillation demonstrate that cardiac arrest is a treatable condition. However, only 31.4% of treated cardiac arrests (84.8% of bystander-witnessed) received bystander CPR. Therefore, ongoing efforts are necessary to encourage the public to be ready, willing, and able to provide CPR when necessary. Further improvements in outcome could be achieved by reducing the time to arrival of EMS providers capable of advanced cardiac life support by improving early detection of cardiac arrest, dispatch protocols, deployment of existing vehicles, number of vehicles available to respond, quality of CPR, and real-time or postevent quality assurance.

CONCLUSION

Out-of-hospital cardiac arrest is a common and lethal event. There are significant and important regional variations in the incidence and outcome of cardiac arrest. Additional investigation is necessary to understand the causes of this variation in an effort to better understand implications for allocation of resources to prehospital emergency care clinical practice and translational cardiac arrest research to reduce the magnitude of this variation and improve cardiovascular health.

Author Contributions: Dr Nichol had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Nichol, Aufderheide, Davis, Idris.

Acquisition of data: Callaway, Hedges, Aufderheide, Brown, Dreyer, Idris, Lowe, Stiell.

Analysis and interpretation of data: Nichol, Thomas, Callaway, Hedges, Aufderheide, Rea, Lowe, Davis, Stiell.

Drafting of the manuscript: Nichol, Thomas.

Critical revision of the manuscript for important intellectual content: Callaway, Hedges, Aufderheide, Rea, Lowe, Brown.

Statistical analysis: Nichol, Thomas.

Obtained funding: Nichol.

Administrative, technical, or material support: Callaway, Hedges, Aufderheide, Brown, Dreyer, Idris, Lowe, Stiell.

Study supervision: Nichol.

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Role of the Sponsor: The funding organizations had no role in the collection, management, analysis, and interpretation of the data or the preparation of the manuscript. A representative of the NIH reviewed and approved the manuscript.

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The world doesn't fear a new idea. It can pigeonhole any idea. But it can't pigeonhole a real new experience.

—D. H. Lawrence (1885-1930)

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Incomplete Financial Disclosures

To the Editor: We are writing to express our regret that we neglected to report financial disclosures in our Commentary on dietary allowance of protein.¹ Dr Wolfe has received an honorarium and expenses for participation in the "Protein Summit 2007: Exploring the impact of high-quality protein on optimal health," with support for the conference provided by the Egg Nutrition Center, National Dairy Council, National Pork Board, and the Beef Checkoff through the National Cattlemen's Beef Association. Dr Miller was formerly employed by the National Cattlemen's Beef Association until her resignation in 2005 and has served as a consultant for the Physicians' Committee for Responsible Medicine in 2006. We apologize to the editors and readers of JAMA for omitting these disclosures and to the extent to which they may reflect a conflict of interest. We hope this information will not affect interpretation of our article. We are not contractually affiliated with and we do not receive any research support from any of the cited organizations.

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Financial Disclosures: Dr Wolfe reported having received an honorarium and expenses for participation in the "Protein Summit 2007: Exploring the impact of high-quality protein on optimal health," with support for the conference provided by the Egg Nutrition Center, National Dairy Council, National Pork Board, and the Beef Checkoff through the National Cattlemen's Beef Association. Dr Miller reported having been formerly employed by the National Cattlemen's Beef Association until her resignation in 2005 and having served as a consultant for the Physicians' Committee for Responsible Medicine in 2006.

1. Wolfe RR, Miller SL. The recommended dietary allowance of protein: a misunderstood concept. *JAMA*. 2008;299(24):2891-2893.

CORRECTIONS

Unreported Financial Disclosures: In the Commentary titled "The Recommended Dietary Allowance of Protein: A Misunderstood Concept" by Wolfe and Miller, published in the June 25, 2008, issue of JAMA (2008;299(24):2891-2893), the financial disclosures for Drs Wolfe and Miller on page 2893 were not reported. The financial disclosures should have read, "Dr Wolfe reported having received an honorarium and expenses for participation in the 'Protein Summit 2007: Exploring the impact of high-quality protein on optimal health,' with support for the conference provided by the Egg Nutrition Center, National Dairy Council, National Pork Board, and the Beef Checkoff through the National Cattlemen's Beef Association. Dr Miller reported having been formerly employed by the National Cattlemen's Beef Association until her resignation in 2005 and having served as a consultant for the Physicians' Committee for Responsible Medicine in 2006."

Incomplete Byline: In the article by Nichol et al titled "Regional Variation in Out-of-Hospital Cardiac Arrest Incidence and Outcome," published in the September 24, 2008, issue (2008;300[12]:1423-1431), the name of the investigator group was omitted from the byline. The end of the byline should have included "for the Resuscitation Outcomes Consortium Investigators." The list of investigators was previously published online in appendix 1 at [http://www.resuscitationjournal.com/article/S0300-9572\(08\)00124-X/addOns](http://www.resuscitationjournal.com/article/S0300-9572(08)00124-X/addOns).

Incorrect Wording: In the Clinical Crossroads article entitled "A 39-Year-Old Man With HIV-Associated Lipodystrophy" published in the September 3, 2008, issue of JAMA (2008;300[9]:1056-1066), an incorrect word changed the meaning of a sentence. On page 1061 under the heading "Thiazolidinediones," the first sentence should have read: "Thiazolidinediones such as rosiglitazone theoretically could affect HIV lipodystrophy as agonists of peroxisome proliferator-activated receptor γ , which influences the transcription of genes regulating adipogenesis and glucose and lipid metabolism, thus potentially leading to increased glucose transport into muscles and increased adipogenesis."⁹³